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**2,454,184**, on December 23, 2003, by **ANDRES M. LOZANO**, for "Method and  
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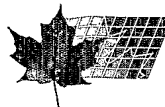
  
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ABSTRACT OF THE DISCLOSURE

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A method of selectively inhibiting or driving neural discharge or activity in or from a specific brain area of a mammal by means of a signal unit means having a CPU processor and signal generator, a surface cortical electrode having a stimulation portion, and a connecting lead, having a proximal end coupled to the signal generator means and a distal portion comprising the electrode; the method comprising (a) locating the stimulation portion of the electrode within the brain parenchyma or adjacent the surface of the brain; (b) coupling the lead to the signal unit means; (c) detecting the pathological intrinsic neural discharges or activity with the electrode to generate a sensor signal within the electrode; (d) analyzing the sensor signal by the signal unit; and (e) prescribing and generating timely electrical pulse stimuli with the signal unit and delivering the impulses to the electrode to alter, block, augment or modify the consequences of the intrinsic neural discharge or activity; wherein the timed pulses are delivered at a time selected from the group consisting of preceding, coinciding with and following said neural discharge or activity. The method and apparatus provides for an improved treatment of neurological disorders particularly movement disorders, such as Parkinson's disease, psychiatric diseases, such as depression, chronic pain disorders, such as post-neural injury pain, and epilepsy, in mammals by electrical stimulation of the brain.

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**METHOD AND APPARATUS FOR TREATING NEUROLOGICAL  
DISORDERS BY ELECTRICAL STIMULATION OF THE BRAIN**

**FIELD OF THE INVENTION**

This invention relates to a method and apparatus for treating neurological disorders, particularly movement disorders, such as Parkinson's disease, psychiatric diseases, such as depression, chronic pain disorders, such as post-neural injury pain, and epilepsy, in mammals by electrical stimulation of the brain.

**BACKGROUND OF THE INVENTION**

Electrical stimulation techniques have become increasingly popular for the treatment of neurological disorders. It has been described to treat movement disorders (US patent number 5,833,709; US patent 6,094,598; US patent 6,356,784; US Patent 6,366,813; US patent 6,484,059); chronic pain (US. Patent 6,505,078); epilepsy (US patent 5,978,702; US patent 5,800,474); psychiatric disorders (US patent 6,609,030; US patent 6,418,344); and to improve cognitive functions (US patent 5,938,688; US patent 6,539,263).

Typically, these stimulation techniques involve the implantation of a signal generator and an implantable electrode, optionally coupled to a sensor. The electrode is implanted in the brain, or over the cortical surface, so that the stimulation portion lies adjacent to a predetermined target. The signal generator is operated to deliver electrical pulses through the electrode at a predetermined rate and amplitude. Stimulators in current clinical use deliver electrical stimulation at a fixed rate (0-185 Hz) with a programmed duty cycle, without adjustment of their output based on intrinsic brain events or activity. However, current brain stimulation systems according to the prior art described for clinical use are not designed or intended to precisely time the delivery of impulses within a critical interval of spontaneous discharges occurring in neurons or groups of neurons in the nervous system.

There still remains a need for an efficacious method for providing improved treatments of neurological disorders in mammals and apparatus for use in said method.

### SUMMARY OF THE INVENTION

5 This invention provides a novel method and device(s) for treating neurological disorders by electrical stimulation of the brain by delivering precisely timed electrical stimuli to a brain area to selectively inhibit or drive the neural activity from the brain area being stimulated. It comprises (a) an array of deep brain or surface cortical surface non-cortical electrodes used to detect intrinsic neural discharges or activity; (b) the use of these same electrodes to deliver precisely timed impulses to precede, coincide with or follow the intrinsic  
10 neural events; and (c) a signal processor unit to (i) analyze the intrinsic neural activity; and (ii) prescribe, generate and deliver an electrical pulse to alter, increment, block or modify the consequences of the intrinsic brain discharge.

Accordingly, in one aspect the invention provides a method of selectively inhibiting or driving neural discharge or activity in or from a specific brain area of a mammal by means  
15 of a signal unit means comprising a central processing unit (CPU) processor means and signal generator means, a surface electrode having a detection and stimulation portion means, and a connecting lead, having a proximal end coupled to said signal generator means and a distal portion comprising said electrode; said method comprising

(a) locating said detection and stimulation portion means of said electrode within the  
20 brain parenchyma or adjacent the surface of the brain, thalamus, brainstem, spinal cord, cranial or peripheral nerves;

(b) coupling said lead to said signal unit means;

(c) detecting the pathological intrinsic neural discharges or activity with said electrode detection portion means to generate a sensor signal within said electrode;

25 (d) analyzing said sensor signal by said signal unit means; and

(e) prescribing and generating timely electrical pulse stimuli with said signal unit means and delivering said impulses to said electrode to alter, block, augment or modify the consequences of said intrinsic neural discharge or activity; wherein said timed pulses are delivered at a time selected from the group consisting of preceding, coinciding with and  
30 following said neural discharge or activity.

Practice of the present invention requires that timing of the interval between pulses is critical. We have found that pulses that occur at intervals of less than about 5 ms cause

inhibition of neural activity, while pulses at intervals greater than about 5 ms cause an increase or facilitation of neural output. According to the invention, pulses delivered through an implanted generator and electrodes can be timed to precisely precede the brain's intrinsic neural firing by 1 to 5 milliseconds in a "preemptive mode". Alternatively, the implanted  
5 generator pulse can be delivered after detecting the brain's own pulse to modify, augment or otherwise alter the brain's activity and effect in a "contingency" mode. In this way, the pathological output of brain areas can be "neutralized" or "altered" and more normal brain function can be restored or neural activity can be increased to enhance neurological function and recovery.

10 The electrodes can be placed on the cortical surface, the subdural or epidural space, or deep within the brain, in for example, the basal ganglia, the subthalamic nucleus, the globus pallidus, a seizure focus, the thalamus or brainstem. They can also be placed atop cranial or peripheral nerves or on the surface of the spinal cord.

The present invention has applications in several disorders, including, but not  
15 restricted to, movement disorders (Parkinson's disease, essential tremor, dystonia) psychiatric disease (depression, mood and anxiety disorders, obsessive compulsive disorders, sleep disorders, substance dependence, schizophrenia), chronic pain disorders (post-stroke pain, post neural injury pain, post-herpetic neuralgia, phantom limb pain) and epilepsy.

Thus, the present invention provides for the focal inhibition or facilitation of neural  
20 activity in human patients by the precisely timed application of neural impulses to the cortical surface of the brain using chronically implanted electrodes. We have found that the application of a single "test" stimulus of, for example, 0.1 to 1 ms duration and of 2 to 5 milliamps to the motor cortex through chronically implanted surface disc electrodes, typically, measuring, for example, 5 mm in diameter and with a 10 mm center to center  
25 separation, produces a motor contraction in the contralateral arm, face, leg or trunk corresponding specifically of what somatotopic motor cortical area is stimulated.

The motor response to this "test" stimulation can also be detected using  
electromyography or EMG, which is a technique capable of detecting minute changes in the electrical activity of muscles. The response in the muscle as measured with EMG is termed a  
30 motor evoked potential or MEP. We have shown that the amplitude of this motor contraction and MEP can be completely abolished or significantly inhibited by applying a preceding sub threshold stimulus, which is insufficient to produce a motor contraction or MEP. This

preceding stimulus is designated a conditioning stimulus because it influences or conditions the effects and consequences of the test stimulus that follows. This effect is very specific in that not just any preceding stimulus will elicit this inhibitory response. We have found that the timing of this preceding stimulus is quite critical and must be at an interval of less than  
5 about 5 ms. In contrast, we have found that stimuli at intervals of greater than about 5 ms and up to 20 to 50 ms, but not longer, have the opposite effect whereby the conditioning stimulus facilitates and enhances the motor contraction and MEP of the test stimulus.

The method can function in a "closed loop" mode using the detected neural discharge as the input which is processed and used to drive a time-locked pulse through the implanted  
10 electrodes and pulse generator.

The invention, thus, also provides said electrical stimulus pulses are time locked to the detected neural discharge such that it precisely preceeds the next intrinsic brain discharge by 1-5 milliseconds to abort or diminish its influence.

Alternatively, the method can be used in "open loop" mode whereby pairs of  
15 electrical stimuli are precisely timed, such as from 1 to 50 milliseconds (ms) apart, to inhibit or increase the amplitude and frequency of discharges from brain targets. In the open loop mode, the pulse output is generated and delivered without using the input detection of a brain event.

The invention, thus, further provides that the electrical stimulus pulses follow the  
20 spontaneous brain activity with an interval of 1 to 50 ms to modify, augment or otherwise alter the consequences of the neural discharge.

The present invention in one aspect thus comprises the application of electrical stimuli either preceding or following an intrinsic spontaneous discharge from a variety of brain areas. The delivered stimuli can precede the intrinsic brain discharge and be considered to act as a  
25 "conditioning" stimulus. Alternatively, the implanted pulse generator stimulus can follow and be delivered on a contingency basis after a detected brain discharge to modify its effect. Further, it is possible to deliver paired pulses to the neural tissue on an ongoing basis independent of the underlying neural activity to alter or disrupt the pathological output of the selected brain area.

The present invention addresses for the first time, the critical role of the specific  
30 temporal patterns of application of stimuli and the effect of altering the output of brain structures by delivering precisely timed small intensity impulses. Such modifying impulses

can be by themselves, sub threshold, that is, that on their own they do not produce an observable effect. When coupled or paired to another stimulus, either one generated by neurons in the brain itself or a stimulus from an implanted pulse generator however, these small stimuli can have profound effects. The maximal inhibitory effects are seen, generally, when a conditioning impulse precedes a second impulse by 1 to 5 milliseconds. On the other hand, delivery of a second impulse at times greater than 5 milliseconds from the first tends to produce an augmentation in the efficacy and clinical effects of the second pulse, a phenomenon which may also serve a therapeutic purpose. In this way, the output of a malfunctioning brain area can be neutralized, modified or altered to improve neurological function. Either the first and/or the second pulse in the sequence can be provided by the implanted pulse generator (designated "P") and electrodes. Either the first or second pulse in a pair sequence can be generated and transmitted through the implanted hardware and be paired and time-locked, preceding or following a spontaneous pulse consisting of the discharge of neurons, from the patient's brain (designated "B"). Thus, the three possible patterns are P-B, B-P and P-P. Varying the spatial distribution, intensity, polarity, frequency in addition to the temporal relationship between two pulse generator stimuli (P-P) or between a stimulus and the spontaneous neural activity of the patient's brain (P-B or B-P) can also be used to optimize clinical effectiveness and decrease the severity of adverse effects of electrical stimulation of the brain.

The methods as hereinabove defined involve the signal unit means having a CPU processor means wherein the signal processor comprises a control algorithm to regulate the generation and delivery of the pulses.

The method preferably involves the step of generating the sensor signal by detecting an electrical or chemical signal or symptom of a movement disorder, pain state or epilepsy discharge and communicating with the control algorithm by telemetry. The detection step according to the invention preferably comprises sensing a physiological symptom of the pain, epilepsy or movement disorder. It, further, preferably comprises adjusting at least one parameter of the stimulation selected from the group consisting of amplitude, pulse width and frequency.

Preferably, operating the signal generator comprises selecting the amplitude, width and frequency of stimulation by the electrode. More preferably, by operating the signal



generator to provide a burst of electrical energy to initiate movement or block an unwanted movement, unwanted epileptic discharge or unwanted pain discharge.

Preferably, the signal generator delivers pulses that are time-locked to within 1 to 50 m/s of a detected neural event and to pulse at a repetition rate of paired pulses at 10-2500 Hertz to augment, block or modulate the neural activity.

In a further embodiment the methods as hereinabove defined comprise

(a) implanting at least one secondary electrode so that a secondary stimulation portion lies in communication with a predetermined portion of said brain;

(b) coupling said secondary electrode to said signal generator; and

(c) operating said signal generator to stimulate said brain.

In a further aspect, the invention provides an apparatus for selectively inhibiting or driving neural activity in or from a specific brain area of a mammal, said apparatus comprising signal unit means comprising signal CPU processor means and signal generator means; a surface electrode having detection and stimulation portion means; connecting lead means having a proximal end coupled to said signal generator and a distal portion comprising or connected to said electrode;

wherein (a) said stimulation portion of said electrode (i) is adapted to be locatable within the brain parenchyma or adjacent the surface of the brain, thalamus, brainstem, spinal cord, cranial or peripheral nerves, (ii) has neural discharge or activity detection means to detect pathological intrinsic neural discharges or activity of said brain area; and (iii) sensor signal generator means to generate a sensor signal;

(b) said signal CPU processor means has

(i) sensor signal analysis means; and

(ii) electrical impulse prescription means; and

(c) said signal generator means comprises means for delivering prescribed said electrical impulses to said electrode at a time selected from the group consisting of preceeding, coinciding with and following said neural discharge or activity to alter, block, augment or modify the consequences of said intrinsic brain discharge or activity.

In a further aspect, the invention as hereinabove defined provides an apparatus wherein said delivery of electrical impulse means comprises means for delivering said impulse that is time locked to the detected neural discharge such that it precisely preceeds the next intrinsic brain discharge by 1-5 milliseconds to abort or diminish its influence.

In a further aspect, the invention as hereinabove defined provides an apparatus wherein said delivery of electrical impulse means comprises means for delivering said impulse follow the spontaneous brain activity with an interval of 5 to 50 ms to modify, augment or otherwise alter the consequences of the neural discharge.

5 In a further aspect, the invention as hereinabove defined provides an apparatus wherein said CPU comprises a control algorithm execution means.

10 In a further aspect, the invention as hereinabove defined provides an apparatus wherein said sensor signal generation means comprises means for detecting a symptom of a movement disorder, pain state or epilepsy discharge and communicating with said control algorithm by telemetry.

In a further aspect, the invention as hereinabove defined provides an apparatus wherein said neural discharge detection means comprises means for sensing a physiological symptom of the pain, epilepsy or movement disorder.

15 In a further aspect, the invention as hereinabove defined provides an apparatus wherein said CPU comprises means of adjusting at least one parameter of the stimulation selected from the group consisting of amplitude, pulse width and frequency to effect regulation.

20 In a further aspect, the invention as hereinabove defined provides an apparatus wherein said CPU comprises means of adjusting at least one parameter of the stimulation selected from timing, amplitude location and duration, to modify neural output.

In a further aspect, the invention as hereinabove defined provides an apparatus wherein said CPU comprises means of selecting amplitude, width and frequency of stimulation by said electrode.

25 In a further aspect, the invention as hereinabove defined provides an apparatus wherein said CPU comprises means for said signal generator to operably provide a burst of electrical energy to initiate movement or block an unwanted movement, unwanted epileptic discharge or unwanted pain discharge.

30 In a further aspect, the invention as hereinabove defined provides an apparatus wherein said CPU comprises means for said signal generator to operably deliver pulses that are time-locked to within 1 to 50 ms of a detected neural event.

In a further aspect, the invention as hereinabove defined provides an apparatus wherein said CPU comprises means for said signal generator to operably pulse at a repetition rate of paired pulses at 10 to 2500 Hertz to augment, block, or modulate said neural activity.

In a further aspect, the invention as hereinabove defined provides an apparatus further comprising at least one secondary electrode

(i) having a secondary stimulation portion adapted to be locatable in communication with a predetermined portion of the brain;

(ii) coupled to said signal unit; and

(iii) adapted to receive electrical pulses from said generator to effect stimulation of said brain.

In a further aspect, the invention as hereinabove defined provides an apparatus wherein said electrode and said secondary electrode comprises an electrode selected from a plurality of electrodes in an array and in communication with said signal unit.

#### BRIEF DESCRIPTION OF THE DRAWINGS

In order that the invention may be better understood, preferred embodiments will now be described, by way of example only, with reference to the accompanying drawings, wherein:-

Fig. 1 is a sketch of an array of electrodes applied to the motor cortical surface of the brain;

Fig. 2 represents a series of electromyography (EMG) graphs showing the amplitude of the motor evoked potential (MEP) under the influence of prior conditioning stimulus delivered at various times;

Fig. 3 is a graph of the ratio of the conditioned MEP to test amplitude against various times of delivery of the conditioning stimulus;

Fig. 4 represents various microelectrode recording of abdominal periodic discharges of individual neurons in the thalamus which cause tremor;

Fig. 5 is an electrocorticogram recorded from electrodes over the surface of the motor cortex in a patient with myoclonus;

Fig. 6 is a sketch of an electrode grid array located in the brain associated with a sensor, signal processor and signal generator;

Fig. 7 is a sketch of a plurality of an alternative electrode arrays located in the brain associated with a sensor, signal processor and signal generator;

Fig. 8 is a diagrammatic cross-section of the brain having an electrode in the thalamus, with associated sensor, signal processor and signal generator;

Fig. 9 is a block diagram of the interrelativity between the electrical/electronic components of use in the invention;

Fig. 10 is a schematic diagram depicting the types of connections between the PPN and related structures within the brain and spinal tissue;  
and wherein the same numerals denote like parts.

#### DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

In a preferred embodiment, the method according to the invention is used to treat tremor conditions with an array or grid of electrodes placed on the motor cortical surface according to Fig 1 wherein an array of 16 electrodes in a 2 by 8 matrix is applied to the surface of the brain or the surface of the dura.

In animal models of tremor disorders, cortical neurons fire in synchrony with a predictable periodicity. In humans, direct measures of neuronal tremor activity have demonstrated that tremor discharges are time locked to peripheral tremor, at a frequency usually from 3 to 15 Hz and are responsible for generating or maintaining the tremor. We have shown that both single unit and field potentials of pathological motor discharges are detectable in humans using either microelectrode recordings or implanted cortical surface electrodes according to Figs. 4 and 5. Abolishing or inhibiting the cortical (or subcortical) tremor discharge and its effects is well known to help the tremor.

As shown in Fig. 2 the amplitude of the motor evoked potential is reduced by a conditioning stimulus delivered 1 ms to 5 ms before. A single stimulus applied to the motor cortex produces a motor contraction and a large motor evoked potential in the contralateral hand muscle (control). If this single stimulus is preceded by a stimulus of lesser intensity delivered 1 to 5 ms before, the amplitude of the motor contraction and MEP is almost abolished or significantly diminished.

As shown in Fig. 3 a conditioning stimulus delivered from 1 to 5 ms before a test stimulus produces an inhibition of the motor evoked potential and a ratio of the conditioned

to test MEP amplitude of less than 100%. On the other hand, at intervals longer than 5 ms and up to 50 ms, there is facilitation (amplitude of MEP over 100%).

Fig. 4 shows abnormal periodic discharges of individual neurons in the thalamus causing tremor are detected with microelectrode recording. These discharges are time locked to tremor and recur with a predictable periodicity such that a pre-emptive pulse could be delivered. Shown is an example in a patient with tremor in Parkinson's disease (PD) and another condition called essential tremor (ET). The tremor in the arm is measured with either an accelerometer (acc) or a electromyogram EMG.

Fig. 5 shows an electrocorticogram recorded from electrodes over the surface of the motor cortex in a patient with myoclonus. The electrode arrays, such as those illustrated in Fig 1 above, can be used to detect pathological discharges from the surface of the brain. In this case from a patient with a form of movement disorder called myoclonus, a condition with similarities to tremor and epilepsy, repetitive pathological discharges are detected using surface electrodes placed over the motor cortical area. The abnormal discharges are detected at specific electrode contacts.

In this embodiment, a patient with tremor would have a craniotomy with placement of surface electrodes over the primary motor area either in the epidural space or directly over the cortical surface. Such an array could have multiple contacts from 4 to 20 in various configurations in, for example, a rectangular 4X5, or 2X8 electrode array, circular, linear or cross shaped. Each contact can be 5 mm in diameter and with a center to center separation of 10 mm. The electrode contacts can be used both to sense neural activity and to deliver electrical impulses. The system has, basically, three major components, namely, 1) the electrodes, 2) a sensor/integrator signal processor and signal generator and 3) an implanted pulse generating device.

Current is delivered through an implantable pulse generator and implanted electrodes overlying the motor cortex of a patient with tremor. If enough current is delivered over the motor cortex, typically over 3 milliamps, motor contractions of the contralateral side of the body are elicited. This "motor mapping" confirms the appropriate placement of the electrode array. The minimum intensity of stimulation required to elicit a motor contraction is designated as the threshold current. As the intensity of this delivered pulse increases, so does the amplitude of the motor contraction and of the MEP.

In a preferred embodiment, a typical sensor, for example, as described in US patent 5,716,377, mentioned hereinabove can detect tremor activity and trigger the pulse generator, which then provides current to the cortical surface a few milliseconds before the next wave of neural activity and, thus, decreasing clinical tremor. In practice, the pathological cortical oscillatory activity that is time locked with the tremor is recorded through the electrodes implanted electrodes. In patients with Parkinson's disease, these rhythmic neural discharges occur with a periodicity of 4-6 times per second (Hz) and are synchronous with the tremor in the extremities. The frequency of tremor varies from patient to patient and according to etiology. Tremor frequency tends to be higher, usually 6-12 Hz, in patients, for example, with the diagnosis of essential tremor. Once this spontaneous activity is identified, sub threshold stimuli, that do not elicit a perceptible effect on their own are applied in a conditioning mode. Conditioning Stimuli (CS) is applied 1 to 5 ms before the predicted next intrinsic pathological brain discharge to inhibit their effect. On the other hand, CS applied later, i.e. more than 5 ms before the intrinsic brain discharge may drive tremor or increase its amplitude. Since tremor activity in several clinical disorders oscillates in predictable frequencies, CS can be applied to the cortical surface 1 to 5 ms before tremor activity, which decreases the clinical manifestations of these conditions.

Aside from tremor, in an alternative embodiment, the method according to the invention discussed can be used to treat other clinical conditions, such as pain, movement disorders, epilepsy, spasticity, and psychiatric disorders. Once a predictable pattern of pathological activity is identified, conditioning stimuli or paired pulses could be provided to decrease the clinical manifestations of the disorders. Examples of abnormal activity that might be detected in order to trigger the delivery of electrical current would be burst of neuronal activity that are synchronous with tremor, so called tremor cells, seizure discharges, and bursting activity in cases of pain, among others.

For the treatment of these different conditions, intraparenchymal, spinal cord, subdural or epidural electrodes, connected to sensing device and a programmable pulse generator, can be used in locations as shown in Figs. 6 - 8.

Referring to Fig. 8, a system or device 16 made in accordance with the preferred embodiment may be implanted below the skin of a patient. A lead 522A is positioned to stimulate a specific site 525 in a brain (B). Device 16 may take the form of a modified signal generator Model 7424 manufactured by Medtronic, Inc. under the trademark Itrel II.

Lead 522A may take the form of any of the leads sold with the Model 7424 such as Model 3387, for stimulating the brain and is coupled to device 16 by a conventional conductor 522.

The distal end of lead 522A terminates in four stimulation electrodes implanted into a portion of the brain by conventional stereotactic surgical techniques.

5 However, other numbers of electrodes, such as two or six, may be used for various applications. Each of the four electrodes is individually connected to device 16 through lead 522A and conductor 522. Lead 522A is surgically implanted through a hole in the skull 123 and conductor 522 is implanted between the skull and the scalp 125 as shown in Fig. 1. Conductor 522 is joined to implanted device 16 in the manner shown. Referring to Fig. 2A,  
10 device 16 is implanted in a human body 120 in the location shown. Body 120 includes arms 122 and 123. Alternatively, device 16 may be implanted in the abdomen.

Conductor 522 may be divided into twin leads 522A and 522B that are implanted into the brain bilaterally as shown. Alternatively, lead 522B may be supplied with stimulating pulses from a separate conductor and signal generator. Leads 522A and 522B could be (1)  
15 two electrodes in two separate nuclei that potentiate each others effects or (2) nuclei with opposite effects with the stimulation being used to fine tune the response through opposing forces.

The targeted treatment site is either the PPN (pedunculo pontine nucleus) or a site that affects the neuronal circuitry as the PPN or a site that affects the same neuronal circuitry of  
20 the PPH. The PPN is the major brain stem motor area and is in a position to control muscle tone, rigidity, posture, balance and locomotion. The PPN consists of a neurochemically and morphologically heterogeneous population of neurons. In the human brain, the PPN is bounded on its lateral side by fibers of the medial lemniscus and on its medial side by fibers of the superior cerebellar penducle and its decussation. Rostrally, the anterior aspect of the  
25 PPN contacts the dorso-medial aspects of the posterolateral substantia nigra (SN), while the retrorubal field borders it dorsally. Caudally, the most dorsal aspect of the PPN is bounded by the cuneiform and subcuneiform nuclei and ventrally by the pontine reticular formation. The most caudal pole of the PPN is adjacent to neurons of the locus ceruleus. Typical stereotaxic coordinates for the PPN in a noral brain are as follows: (1) medial-lateral  
30 dimension 2 to 12 mm; dorsal-ventral dimension-6 to -18 mm; and anterior-posterior dimension -2 to -12 mm. (The medial-lateral dimensions are relative to midline of the brain; the anterior-posterior dimensions are relative to the midpoint between the anterior

commissure and posterior commissure with negative indicating the posterior direction; the dorsal-ventral dimensions are relative to a line connecting the midpoints of the anterior and posterior commissures with negative being ventral to the line).

The PPN generally consists of two subdivisions characterized by cell density. The pars compacta of the PPN (PPNc) is located with the caudal half of the nucleus in the dorsolateral aspect. Cells of the subnucleus pars dissipatus (PPNd) are distributed sparsely with the superior cerebellar peduncle and central tegmental tract. Cholinergic PPNc neurons are clustered along the dorsolateral border of the superior cerebellar peduncle (SP) at trochlear nucleus levels, whereas those in the PPNd are scattered along the SP from the midmesencephalic to midpontine levels. In the human brainstem, the cholinergic neuronal population of the PPN constitutes more than 90% of the neuronal population of the PPNc, whereas this percentage varies from 25% to 75% in the PPNd. A second prominent neuronal population contained within the PPNd is glutamatergic. Other neuronal types within the PPN may include dopaminergic neurons, noradrenergic neurons, and GABA-ergic interneurons.

As shown in Fig. 10, certain relationship exists between the PPN and various structures of the basal ganglia. The PPNd, for example, provides excitatory glutamatergic outputs to many targets including the substantia nigra, the globus pallidus, the subthalamic nucleus and to brainstem centers and the spinal cord. Knowledge of these relationships may be utilized to provide treatment therapies for various disorders by targeting the PPN.

The stimulation administered by device 16 to the PPN depends on the specific movement disorder that is to be treated and the effect that the stimulation has on other parts of the brain. For example, PPNc neurons provide cholinergic inputs to the thalamus and the SNc and receive important sensory feedback information from the spinal chord. Thus, stimulation to influence PPNc cholinergic neurons may be useful for modulation of steady-state locomotion. As another example, stimulation using a high frequency to block the output of the PPNc, thereby decreasing the excitatory input to the VL thalamus, would help treat hyperkinetic movement disorders. On the other hand, stimulation with a low frequency to facilitate the excitatory output of PPNc would alleviate symptoms for persons with hypokinetic movement disorders. Glutamatergic PPNd neurons receive outputs from the main subthalamic nucleus (STN), the internal globus pallidus (Gpi), and the substantia nigra pars reticulata (SNr) and provide the main outflow of information to the spinal chord. Thus, stimulation to influence PPNd glutamatergic neurons may be useful for the control of



initiation of locomotion. Further, the stimulation parameters may vary depending upon the type of neurons in the PPN that should be stimulated. To elicit locomotion, continuous mid-frequency stimulation on the order of 20 – 60 Hertz may be used. To reduce muscle tone, high frequency stimulation (greater than 100 Hertz) may be used.

5 In another embodiment according to the invention, stimulation can be provided to interconnected anatomical structures to modulate the activity of distant brain region of interest. The electrode in this case is implanted in a region different from the one implied in the mechanisms of the disease. If the connection between these two structures is inhibitory, inhibitory paired pulses can be applied to reduce the inhibitory outflow from this area, with a  
10 consequent increase in the activity in the downstream target that is responsible for producing the patients symptoms. The opposite can be expected with excitatory connections.

In another embodiment, according to the invention, current can be applied to the neural tissue in order to induce plasticity, either long-term depression or long term potentiation. With prolonged stimulation applied to neural tissue, several biochemical and  
15 physiological reactions occur that produce long lasting changes in neuronal connectivity and synaptic transmission efficiency. These changes involve changes in gene expression and morphological modifications in the neurons being stimulated. Sub threshold current can be applied to induce synaptic plasticity. Delivery of these plasticity inducing pulses in a manner that is time locked to a spontaneous brain discharge can modify, either potentiate or block  
20 neural plasticity.

Fig. 9 shows generally as 100, electrode detector, sensor signal generator and stimulator, 102 linked to signal CPU processor 104 and signal generator 106. CPU processor 104 has a control algorithm and its execution means comprising sensor signal analyzer means and prescriber algorithms, which, respectively, analyze the electrode detector signal 108 and  
25 prescribe the characteristics 110 of the electric pulse 112 to be generated by generator 106 and fed to electrode 102.

Fig. 10 shows the major connections between PPN – Basal Ganglia and related structures in the primate.

In summary, the present invention uses stimulation in a precise pattern that is time  
30 locked within a few milliseconds of a spontaneous neural discharge. This mode of stimulation alters the pathologic output of the brain and enhance neural function. A further benefit is that

because stimulation can be applied on a contingency basis, only if and when required, there is less energy requirements and a prolongation in the life of implanted batteries.

Although this disclosure has described and illustrated certain preferred embodiments of the invention, it is to be understood that the invention is not restricted to those particular  
5 embodiments. Rather, the invention includes all embodiments which are functional or mechanical equivalence of the specific embodiments and features that have been described and illustrated.

**Claims:**

1. A method of selectively inhibiting or driving neural discharge or activity in or from a specific brain area of a mammal by means of a signal unit means comprising a CPU processor means and signal generator means, a surface electrode having a detection and stimulation portion means, and a connecting lead, having a proximal end coupled to said signal generator means and a distal portion comprising said electrode; said method comprising
  - (a) locating said detection and stimulation portion of said electrode within the brain parenchyma or adjacent the surface of the brain, thalamus, brainstem, spinal cord, cranial or peripheral nerves;
  - (b) coupling said lead to said signal unit means;
  - (c) detecting the pathological intrinsic neural discharges or activity with said electrode to generate a sensor signal within said electrode;
  - (d) analyzing said sensor signal by said signal unit means; and
  - (e) prescribing and generating timely electrical pulse stimuli with said signal unit means and delivering said impulses to said electrode stimulation portion to alter, block, augment or modify the consequences of said intrinsic neural discharge or activity; wherein said timed pulses are delivered at a time selected from the group consisting of preceding, coinciding with and following said neural discharge or activity.
2. A method as defined in claim 1 wherein said electrical pulse is time locked to the detected neural discharge or activity such that it precisely precedes the next intrinsic brain discharge or activity by 1-5 milliseconds as to abort or diminish the influence of said discharge or activity.
3. A method as defined in claim 1 wherein said electrical pulse follows the spontaneous brain activity with an interval of 1 to 50 ms to modify, augment or otherwise alter the consequences of the neural discharge.
4. A method as defined in any one of claims 1 to 3 wherein said signal CPU processor means comprises a control algorithm, and further comprises executing said control algorithm to regulate said generation and delivery of said pulses.
5. A method as defined in any one of claims 1 to 4 wherein said generation of said sensor signal comprises detecting a symptom of a movement disorder, pain state or epilepsy discharge and communicating with said control algorithm by telemetry.

6. A method as defined in any one of claims 1 to 5 wherein said detection comprises sensing a physiological symptom of the pain, epilepsy or movement disorder.

7. A method as defined in any one of claims 1 to 6 comprising adjusting at least one parameter of the stimulation selected from the group consisting of amplitude, pulse width and frequency.

8. A method as defined in claim 7 further comprising adjusting at least one parameter of the stimulation selected from timing, amplitude, location and duration to modify neural output.

9. A method as defined in any one of claims 1 to 8 comprising selecting amplitude, width and frequency of stimulation by the electrode.

10. A method as defined in any one of claims 1 to 9 comprising operating the signal generator to provide a burst of electrical energy to initiate movement or block an unwanted movement, unwanted epileptic discharge or unwanted pain discharge.

11. A method as defined in any one of claims 1 to 10 comprising operating said signal generator to deliver pulses that are time-locked to within 1 to 50 ms of a detected neural event.

12. A method as defined in any one of claims 1 to 11 comprising operating said signal generator to pulse at a repetition rate of paired pulses at 10-2500 Hertz to augment, block or modulate said neural activity.

13. A method as defined in any one of claims 1 to 12, comprising:

(a) implanting at least one secondary electrode so that a secondary stimulation portion lies in communication with a predetermined portion of said brain;

(b) coupling said secondary electrode to said signal generator; and

(c) operating said signal generator to stimulate said brain.

14. A method as defined in any one of claims 1 to 13 wherein said electrode comprises an electrode selected from a plurality of electrodes in an array and in communication with said signal unit.

15. Apparatus for selectively inhibiting or driving neural activity in or from a specific brain area of a mammal, said apparatus comprising  
signal unit means comprising signal CPU processor means and signal generator means;  
a surface electrode having a detection and stimulation portion;

connecting lead means having a proximal end coupled to said signal generator and a distal portion comprising or connected to said electrode;

wherein (a) said stimulation portion of said electrode (i) is adapted to be locatable within the brain parenchyma or adjacent the surface of the brain, thalamus, brainstem, spinal cord, cranial or peripheral nerves; (ii) has neural discharge or activity detection means to detect pathological intrinsic neural discharges or activity of said brain area; and (iii) sensor signal generator means to generate a sensor signal;

(b) said signal CPU processor means has

(i) sensor signal analysis means; and

(ii) electrical impulse prescription means; and

(c) said signal generator means comprises means for delivery said prescribed electrical impulses to said electrode at a time selected from the group consisting of preceding, coinciding with and following said neural discharge or activity to alter, block, augment or modify the consequences of said intrinsic brain discharge or activity.

16. Apparatus as defined in claim 15 wherein said delivery of prescribed electrical impulse means comprises means for delivering said impulse that is time locked to the detected neural discharge such that it precisely preceeds the next intrinsic brain discharge by 1-5 milliseconds to abort or diminish its influence.

17. Apparatus as defined in claim 15 wherein said delivery of electrical impulse means comprises means for delivering said impulse follow the spontaneous brain activity with an interval of 5 to 50 ms to modify, augment or otherwise alter the consequences of the neural discharge.

18. Apparatus as defined in any one of claims 15 to 17 wherein said CPU comprises control algorithm execution means.

19. Apparatus as defined in any one of claims 15 to 18 wherein said sensor signal means comprises means for detecting a symptom of a movement disorder, pain state or epilepsy discharge and communicating with said control algorithm by telemetry.

20. Apparatus as defined in any one of claims 15 to 19 wherein said neural discharge detection means comprises means for sensing a physiological symptom of the pain, epilepsy or movement disorder.

21. Apparatus as defined in any one of claims 15 to 20 wherein said CPU comprises means of adjusting at least one parameter of the stimulation selected from the group consisting of amplitude, pulse width and frequency to effect regulation.

22. Apparatus as defined in any one of claims 15 to 21 wherein said CPU comprises means of adjusting at least one parameter of the stimulation selected from timing, amplitude location and duration, to modify neural output.

23. Apparatus as defined in any one of claims 15 to 22 wherein said CPU comprises means of selecting amplitude, width and frequency of stimulation by said electrode.

24. Apparatus as defined in any one of claims 15 to 23 wherein said CPU comprises means for said signal generator to operably provide a burst of electrical energy to initiate movement or block an unwanted movement, unwanted epileptic discharge or unwanted pain discharge.

25. Apparatus as defined in any one of claims 15 to 24 wherein said CPU comprises means for said signal generator to operably deliver pulses that are time-locked to within 1 to 50 ms of a detected neural event.

26. Apparatus as defined in any one of claims 15 to 25 wherein said CPU comprises means for said signal generator to operably pulse at a repetition rate of paired pulses at 10 to 2500 Hertz to augment, block, or modulate said neural activity.

27. Apparatus as defined in any one of claims 15 to 26 further comprising at least one secondary electrode

(i) having a secondary stimulation portion adapted to be locatable in communication with a predetermined portion of the brain;

(ii) coupled to said signal unit; and

(iii) adapted to receive electrical pulses from said generator to effect stimulation of said brain.

28. Apparatus as defined in any one of claims 15 to 27 wherein said electrode and said secondary electrode comprise electrodes selected from a plurality of electrodes in an array and in communication with said signal unit.

FIG 1

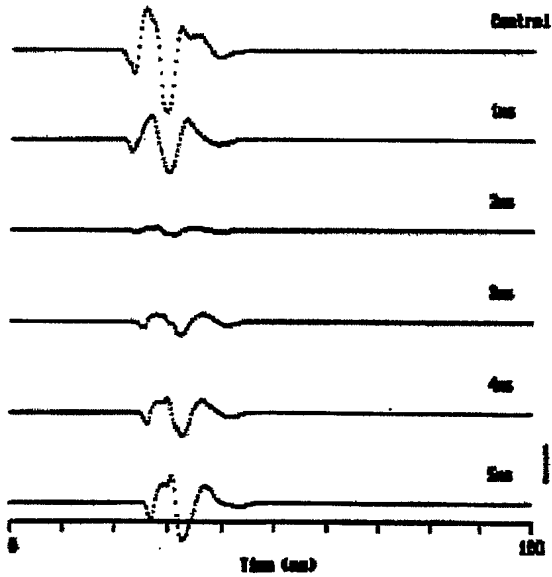
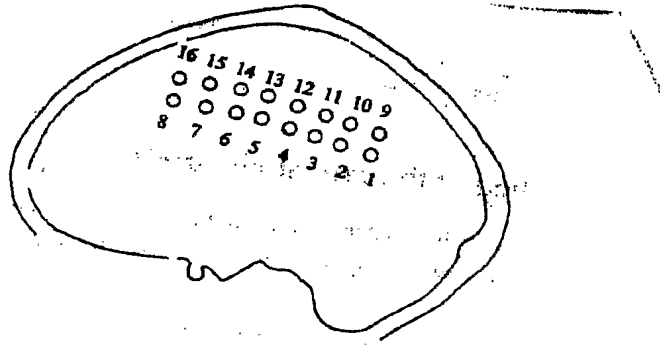


FIG 2

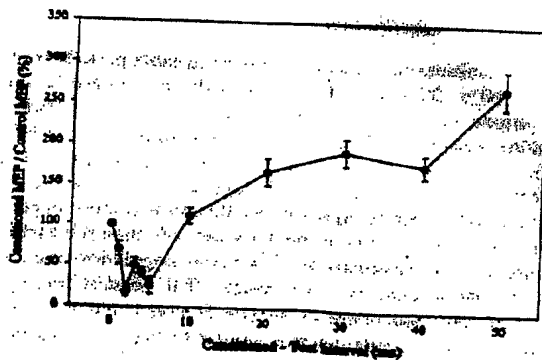


FIG 3

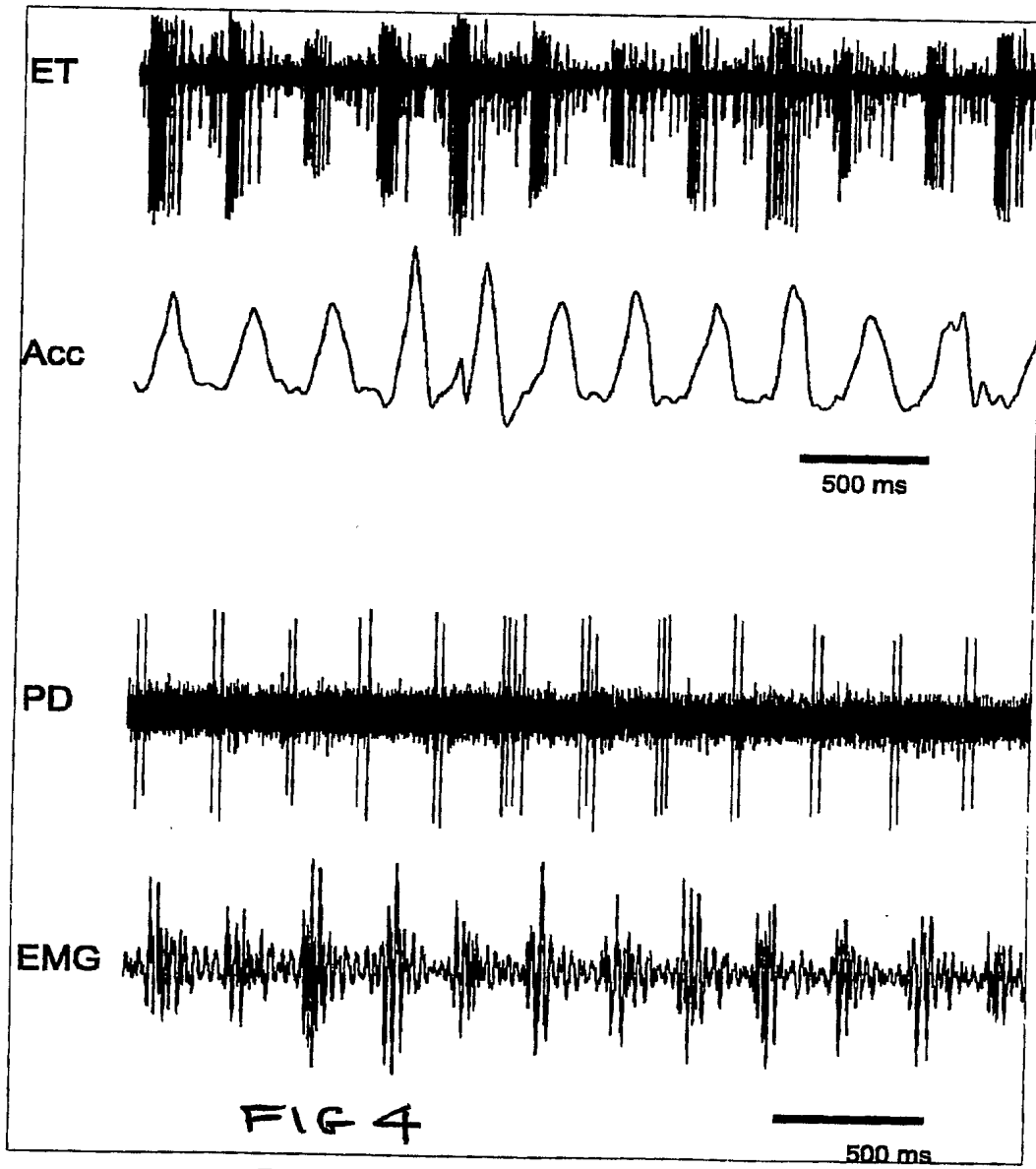




FIG 5

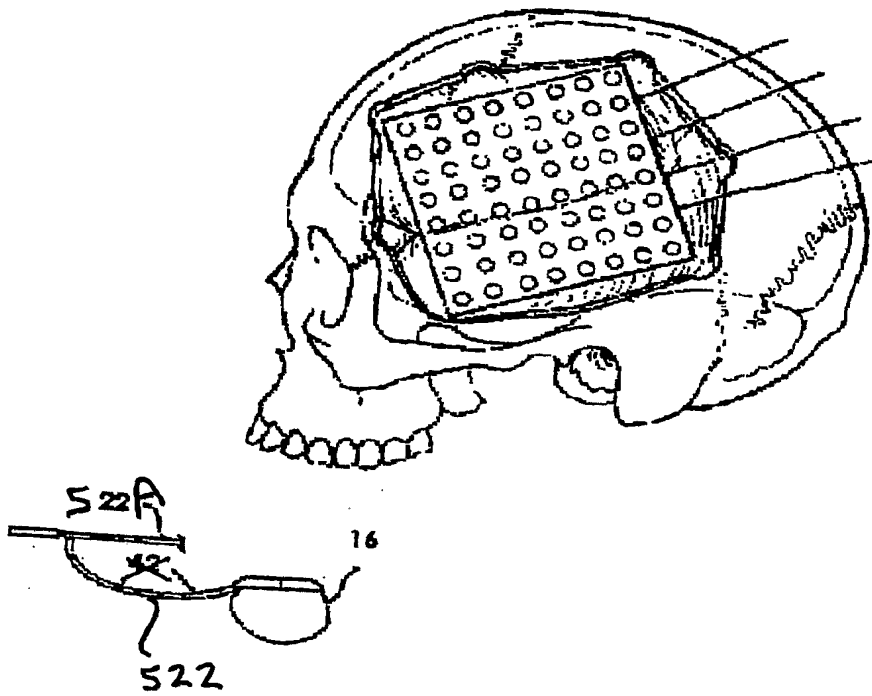
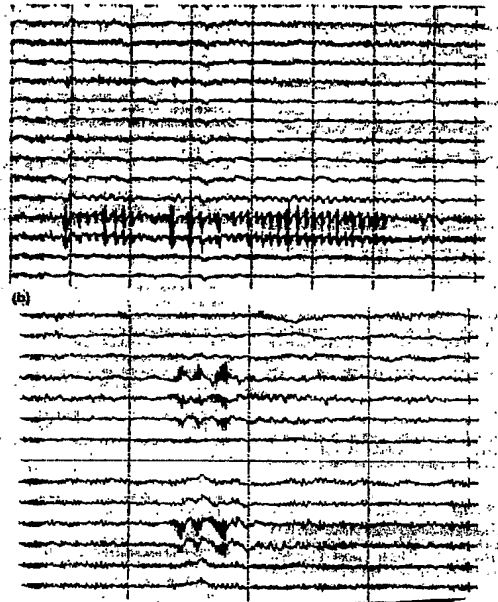


FIG 6

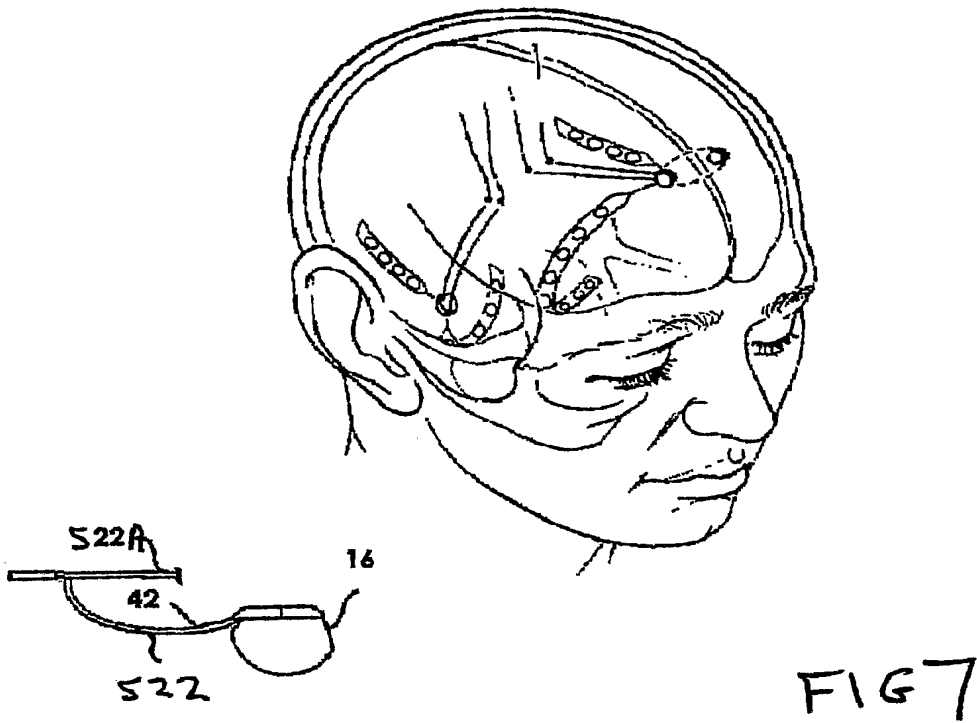
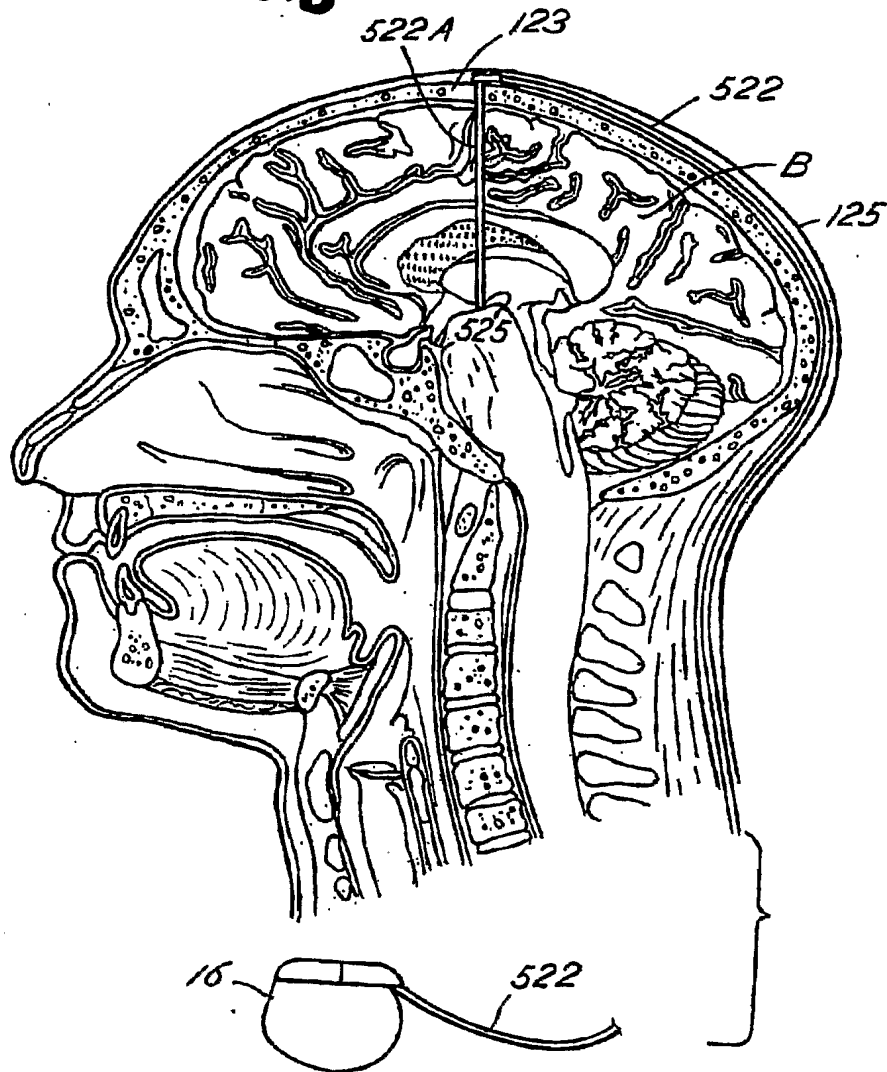


FIG. 8



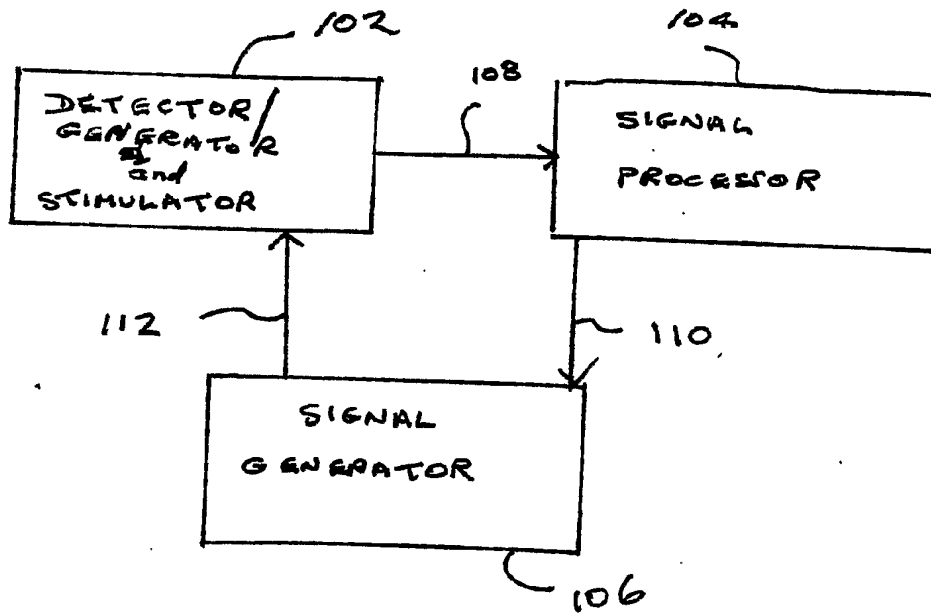


FIG 9

FIG.1D

